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Selecting a Calcium Channel-Blocking Agent

SUMMARY

The three currently available channel-blocking agents, nifedipine (Adalat), diltiazem (Cardiazem), and verapamil (Isoptin), are all useful in treating a number of cardiovascular disorders, especially ischemic heart disease. Although they have a common mechanism of action, their cardiovascular effects and pharmacological properties differ considerably. Each drug, consequently, has specific clinical indications; these drugs are not easily interchangeable. Understanding their properties and effects allows the physician to choose the particular drug most suited to the patient's needs. (*Can Fam Physician* 1987; 33:1019–1023.)

RÉSUMÉ

Il existe actuellement sur le marché trois bloqueurs des canaux calciques, la nifédipine (Adalat), le diltiazem (Cardiazem) et le vérapamil (Isoptin) qui sont utiles dans le traitement d'un certain nombre de maladies cardiovasculaires, plus particulièrement dans la cardiopathie ischémique. Bien que leur mécanisme d'action soit semblable, leurs effets cardiovasculaires et leurs propriétés pharmacologiques diffèrent considérablement. Conséquemment, chaque médicament comporte des indications cliniques spécifiques; ces médicaments ne sont pas facilement interchangeables. La compréhension de leurs propriétés et de leurs effets permettra au médecin de choisir le médicament qui convient le mieux aux besoins de son patient.

Key words: calcium channel-blocking agents, cardiovascular disorders, ischemic heart disease

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THE THREE currently available channel blocking agents, nifedipine (Adalat), diltiazem (Cardiazem), and verapamil (Isoptin), are all useful in treating a number of cardiovascular disorders, especially ischaemic heart disease. While all three agents have a common mechanism of action, their cardiovascular effects and pharmacological properties differ considerably.

Mechanism of Action and Cardiovascular Effects

Calcium channel blockers work by inhibiting Ca^{++} movement across the cell membrane during depolarization in smooth and cardiac muscle. This action blocks muscle contraction and results in decreased myocardial contractility and decreased smooth muscle cell tone (vasodilation).[1] Generation and conduction of impulses in the sinoatrial (SA) and atrioventricular (AV) nodes of the heart depend on the movement of Ca^{++} through membrane channels. Calcium channel blockers therefore slow conduction and can inhibit impulse formation. Each calcium blocker creates a balance of these three properties and reflex effects.

Nifedipine is an extremely potent vasodilator; it is much more powerful than diltiazem or verapamil.[2] The vasodilation it produces elicits a strong reflex sympathetic response which completely overwhelms its effect on cardiac conduction and contractility. Nifedipine, therefore, has no effect on arrhythmias; the increased sympathetic tone that its use produces may result in increased heart rate.[3]

Verapamil, in contrast, has a much stronger effect on cardiac conduction than it has on vasodilation. When verapamil is given in clinical doses, its reflex sympathetic effects do not overcome its tendency to slow cardiac conduction and decrease myocardial function.[4] The net result is decreased heart rate and myocardial contractility. Verapamil can therefore be used as an antiarrhythmic agent that has no major effects on blood pressure.[5]

Diltiazem falls between nifedipine and verapamil. It has less direct effect on AV conduction than has verapamil, but it is a relatively weak peripheral vasodilator, and so its net effect is to cause slowing of the heart rate. It has little, if any, effect on cardiac contractility, but it is as potent a coronary vasodilator as verapamil.

Pharmacology and Drug Interactions

Calcium channel blockers will often be prescribed for patients already on one or more cardiac drugs. Several interactions will alter or determine their choice or administration.

Nifedipine and verapamil both result in increased digoxin levels when given to a patient receiving digoxin, probably as a result of decreased renal

excretion.[6] It is particularly important for the physician to consider this effect as it relates to verapamil, since both verapamil and digoxin prolong AV conduction. A patient given verapamil who subsequently became digoxin toxic could suffer severe bradycardia or high-grade AV block.

Diltiazem does not produce as consistent an effect on serum digoxin levels as do the other calcium channel blockers, but it may have an additive effect in prolonging AV conduction. Hence it, too, must be used with caution in patients receiving digoxin. Generally speaking, maintenance doses of digoxin should be decreased by 50% when verapamil or nifedipine is added. As a minimum precaution, serum digoxin levels should be monitored frequently.

Calcium channel blockers are often prescribed for patients with chronic stable angina who are refractory to nitrates and beta blockers. Calcium channel blockers and beta blockers can be combined safely and with good therapeutic outcome, but not in all patients. Because both beta blockers and verapamil exert negative inotropic, chronotropic and dromotropic effects, these drugs generally should not be used in combination, especially in patients with depressed left ventricular function or abnormalities of impulse generation or conduction. Congestive heart failure, bradycardia or hypotension might result.[1]

If these two classes of drugs are used together, nifedipine appears to be the safest choice among the calcium channel blockers.[7] It has less deleterious effect on myocardial contractility or cardiac conduction than does verapamil or diltiazem. Although adverse reactions attributable to the combination are uncommon, hypotension and exacerbation of congestive failure have been reported.[8] In patients prescribed a combination of beta blockers with diltiazem, AV block and heart failure occur rarely and sinus bradycardia infrequently.[9]

Combining these drugs is probably safe if there is no evidence of left ventricular dysfunction (that is, if there are no findings on history or physical examination suggestive of congestive failure or ejection fraction known to be greater than 30%), if the dose of beta blocker is relatively low, and if the patient is followed closely.[10]

Intravenous verapamil is contraindicated in patients on beta blockers because of problems with excessive prolongation of AV conduction, which might cause bradycardia or asystole. With oral administration adverse reactions are largely hemodynamic rather than electrophysiologic.

Precautions and Contraindications

Diltiazem and verapamil, because of their effect on AV conduction, are contraindicated in patients with sick sinus syndrome, AV block greater than first degree, or digoxin toxicity.

Generally, verapamil should be avoided in patients being treated with type-1 antiarrhythmics, especially disopyramide, because the combined negative inotropic effect may give rise to congestive heart failure. Verapamil has extensive first pass hepatic metabolism, and so patients with hepatic dysfunction or on other medication that affects hepatic blood flow (e.g., cimetidine) may require reduced doses.[11]

Nifedipine is contraindicated in patients with hypotension or digitalis toxicity, in the latter case because it will diminish digoxin excretion. All three drugs should be avoided in patients with congestive failure. Nifedipine has been used as an afterload-reducing agent in some patients with congestive failure; although it has minimal negative inotropic effect in small doses, safer alternatives are generally available.

Adverse Effects and Dosage Recommendations

Adverse effects of oral and intravenous verapamil occur in approximately 10% of patients.[5] Side-effects occurring with parenteral administration derive from the drug's action on the myocardial conduction system, ventricular pump function and peripheral vascular tissue. A slight fall in arterial pressure commonly occurs with therapeutic doses of the drug, but severe or troublesome hypotension is rare. Electrophysiologic toxicity (SA or AV node suppression) will usually be seen before significant myocardial depression unless ventricular function is markedly abnormal. Serious side-effects of intravenous verapamil, such as hypotension, bradycardia and even asystole, have been seen, but usually in patients receiving concomitant beta blockade or in patients with severe hypertrophic cardiomyopathy.[1]

Oral verapamil is well tolerated, producing a fairly low prevalence of gastrointestinal intolerance and constipation, vertigo, headache and nervousness. Many of these side-effects subside with continued therapy.[5] Late adverse effects include ankle edema not associated with congestive heart failure, constipation and postural hypotension.

The usual starting dose of oral verapamil is 80 mg three to four times daily with titration over several days to a maximum of 480 mg per day.

The most common side-effect of nifedipine is headache, which occurs in approximately 6% of patients.[12] Other common side-effects are caused primarily by the drug's vasodilator properties; they include feelings of warmth, flushing, dizziness, palpitations and hypotension. Nausea and vomiting occur occasionally. Pedal edema unrealted to congestive heart failure is a common late adverse effect. Adverse effects occur in about 15%−17% of patients.

The usual starting dose of nifedipine is 10 mg given three or four times daily. The dose may be increased, depending on clinical response, to a maximum recommended dose of 120 mg daily.

Diltiazem is very well tolerated, though conduction abnormalities, vasodilation and hypotension can occur. Drug rash, dizziness, flushing, headache and gastrointestinal upset have been reported in some patients. Diltiazem does not produce constipation and rarely exacerbates congestive heart failure. It has been suggested that side-effects are less frequent with diltiazem than with other calcium channel-blocking agents because diltiazem may cause relatively less peripheral vasodilation for the same degree of coronary vasodilation and may therefore produce less autonomic activation.[13]

The usual starting dose of diltiazem is 30 mg four times daily. This dose is rapidly increased to 60 mg four times daily if the drug is well tolerated. The maximum recommended dose is 360 mg daily.

Clinical Applications of Calcium Channel-Blocking Agents

Variant angina

Variant, or Prinzmetal's, angina is the syndrome in which patients have chest pain at rest, associated with re-

versible S-T segment elevation. Coronary artery spasm is associated with this syndrome, which may be present with or without organic obstructive lesions.[14] Transient impairment of coronary blood flow secondary to spasm is the most common cause of spontaneous, postprandial, nocturnal and cold-induced angina.[15] Typical angina that occurs early in the morning or when the patient is at rest is also suggestive of spasm.

The exact cause of coronary spasm is unknown; vascular, neurohumeral and platelet factors may all contribute. The final common pathway may be via increased intracellular calcium which is responsible for contraction and tone of vascular smooth muscle.[16] The probable mechanism by which calcium channel-blocking agents work in variant angina is the decrease of the inappropriately stimulated tone of arterial smooth muscle during coronary vasospasm.[14]

Verapamil, nifedipine and diltiazem are all effective in treatment of coronary spasm. These drugs reduce the frequency of anginal attacks, the amount of nitroglycerin consumed, the number of symptomatic and asymptomatic ST-segment elevations, and the number of hospitalizations.[16] Not only are attacks of angina at rest abolished or markedly reduced in frequency, but the life-threatening episodes of ventricular tachyarrhythmias that often accompany the episodes of spasm are often eliminated, presumably through amelioration of the ischemia responsible for the electrical instability.[17]

Most of the studies showing the efficacy of calcium channel blockers in variant angina were not controlled, but the results are nonetheless impressive, since many of the patients were resistant to other forms of treatment. In 20 studies of 561 patients who received one of these drugs, 68% of patients gained complete control of clinical manifestations of the disease, and a further 22% showed improvement of greater than 50%. Only 10% were non-responders. Clinical results appear slightly better with nifedipine and diltiazem: 73% of patients studied became completely asymptomatic.[16]

There are few studies that directly compared the efficacy of the various calcium channel blockers in the treatment of variant angina, but there is some suggestion that verapamil is the least effective drug, possibly because it is the least potent for inducing relaxation of coronary vasculature.

Nitrates provide effective treatment for variant angina, but calcium channel blockers may be effective when nitrates are not.[14] Combination therapy with these two classes of drugs seems to be more effective than use of either agent alone.[18] Calcium channel blockers are probably the drugs of choice for variant angina, and they are certainly indicated if long-acting nitrates fail to control symptoms.

Chronic stable angina

There is a large body of evidence to show that calcium channel blockers are as effective as long-acting nitrates and beta blockers in treatment of classic, stable, effort-induced angina accompanied by exercise-induced ST-segment depression that is associated with obstructive coronary artery disease.

The imbalance between myocardial oxygen supply and demand, which is responsible for ischemia in stable angina, can be relieved by increasing supply, reducing demand, or both. There is evidence supporting both modes of action in treatment of stable angina.[2] By decreasing peripheral vascular resistance or afterload (with all agents) and decreasing myocardial contractility and heart rate (with verapamil and diltiazem), the agents decrease myocardial oxygen consumption. Since inappropriate coronary vasoconstriction may contribute to the production of myocardial ischemia in patients with classic angina pectoris, coronary arterial vasodilation is another mechanism by which calcium channel blockers may be effective in treatment of stable angina.

There are few comparisons of the various calcium channel-blocking agents in patients with stable angina, and the relative effectiveness of these agents in this setting is likely to remain an area of controversy.

A composite analysis of 190 patients treated with nifedipine from eight double-blind placebo-controlled studies indicates that, although use of this drug reduces exertional angina in most patients, anginal symptoms may increase in up to 11% of patients. The reflex increase in myocardial contractility or heart rate, or both, secondary to excessive reduction in afterload, may be responsible for the imblance between oxygen supply and demand. Alternatively, collateral coronary flow may be redistributed, giving rise to coronary steal.[19] Nifedipine is the safest choice among the calcium channel blockers for combination with beta blockers, and optimal treatment with nifedipine in patients with effort angina appears to require treatment with a beta blocker to avoid a paradoxical exacerbation of angina. It has also been shown that nifedipine, along with verapamil and diltiazem, has additional therapeutic effects when used with propranolol for patients with chronic stable angina.

In the medical management of all patients with stable angina, sublingual nitroglycerin is used to treat episodes of angina or to prevent angina in situations known to precipitate it. A long-acting nitrate is generally the next step in therapy. If pain relief is incomplete, a beta blocker or calcium channel blocker is added. When treatment of stable angina with beta blockers is relatively contraindicated (e.g., in patients with peripheral vascular disease, congestive heart failure, asthma, obstructive airways disease, SA- or AV-node disease, or in patients known to have adverse central nervous system effects from beta blockers), a calcium channel blocker is the drug of choice.

For patients with obstructive airways disease, peripheral vascular disease or diabetes, diltiazem or verapamil should be added if treatment with nitrates alone is unsatisfactory. For patients with SA- or AV- block, nifedipine would be the calcium channel blocker of choice. For those with diabetes or intermittent claudication in whom nitrates and a calcium channel blocker were ineffective, a beta blocker could be added, with caution, in an attempt to avoid surgical intervention. For patients with severe obstructive airways disease or SA- or AV-node disease whose angina is not controlled with dual therapy, the risks of beta blockade may outweigh the risks of a revascularization procedure, and referral for coronary arteriography should be considered.

For patients with congestive heart failure and angina not controlled by nitrates, nifedipine may be tried in low doses, since the dose of nifedipine that causes vasodilation and afterload reduction is less than that which depresses the myocardium.[14] These patients must be monitored very carefully. Failure of nifedipine to produce improvement in anginal symp-

toms would constitute an indication to consider angiography.

Patients with angina and hypertension are best treated with beta blockers if nitrates are insufficient. Nifedipine would be added next. If hypertension and angina both remain uncontrolled, therapy involving vasodilator or angiotension-converting enzyme inhibitor should be tried before assessment for a revascularization procedure.

For patients with angina that is severe enough to require therapy with more than a single drug, but without specific contraindication to any antianginal agent, the combination of a beta blocker with nifedipine is appropriate. An alternative treatment is the combination of verapamil with a long-acting nitrate. Both verapamil and beta blockers produce negative inotropic effects and depress automaticity, while both nifedipine and nitrates are potent vasodilators; these drug combinations, therefore, may potentiate adverse effects.

The reported incidence of side-effects with use of diltiazem has been very low. This suggests that this drug might be considered as monotherapy in many patients with angina who are intolerant of other drugs.[2]

Unstable angina pectoris

Patients with rest angina may have a wide spectrum of disorders ranging from variant angina with ST-segment elevation associated with relatively normal coronary arteries to unstable angina with ST-segment depression or elevation associated with multivessel coronary artery disease.[10] In either case coronary spasm, possibly superimposed on atherosclerosis, is an important mechanism, and calcium channel blockers might therefore be expected to constitute effective treatment.[20]

Patients are usually hospitalized, monitored and given medications intravenously. Nitrates are given initially and may be followed by calcium channel blockers, all of which have been shown to be effective, even for patients with continued clinical instability, despite the use of nitrates and beta blockers. Beta blockers are used, but may cause coronary spasm through unopposed alpha adrenergic stimulation of the coronary vessels.

Studies of the long-term effectiveness of calcium channel blockers in patients with unstable angina indicate that the drugs appear to reduce the number of patients who require bypass surgery for relief of angina, but do not appear to alter the frequency of myocardial infarction or sudden death.[21]

Arrhythmias

Paroxysmal supraventricular tachycardia. Verapamil has become the treatment of choice in re-entrant supraventricular tachycardia.[22] Nifedipine and diltiazem have not been used therapeutically.[23] Verapamil is effective in treatment of paroxysmal supraventricular tachycardia because it prolongs AV-nodal conduction and increases the AV-nodal refractory period.[13]

For termination of atrial arrhythmias the most commonly used dose of verapamil is an injection of 5–10 mg (or 0.15 mg/kg) over a 60-second period, with ECG and blood-pressure monitoring.[5] If the injection does not terminate the arrhythmias or cause untoward effects, a similar dose to a maximum of 15 mg, may be administered 30 minutes later.

Approximately 80% of cases will convert to sinus rhythm, and 10% will have a decrease in rapid ventricular rate. An oral maintenance dose of 120 mg three times daily will help to prevent recurrences, but is no more efficacious than other prophylactic agents.[13]

Atrial Fibrillation. For patients with atrial fibrillation verapamil has been shown to be effective in controlling the ventricular response quickly and safely.[24] In a few patients it has succeeded in restoring sinus rhythm. Intravenous administration is generally carried out as described for paroxysmal supraventricular tachycardia. The dose required may vary with the hemodynamic state of the patient.[23] Increased sympathetic tone, as seen in congestive failure, may reduce the slowing of ventricular rate.

Oral verapamil by itself or with digoxin, may help to control atrial fibrillation when the ventricular response is poorly controlled by conventional means, when the ventricular rate escapes with exercise, or when other commonly used medications may be contraindicated.[25] Oral verapamil is not effective in preventing recurrent episodes of atrial fibrillation.

Atrial Flutter. Verapamil is rarely effective in the conversion of atrial flutter to sinus rhythm, but is generally effective in control of ventricular response through its negative dromotropic effect. Oral verapamil is not effective in preventing recurrent episodes of atrial flutter, but may be a useful supplement to digitalis for controlling a rapid ventricular rate in patients with this arrhythmia.[13]

Wolff-Parkinson-White Syndrome. Caution must be advised in the use of all drugs that depress AV nodal conduction in WPW syndrome. By prolonging AV nodal conduction in the presence of supraventricular tachycardia, verapamil may increase anterograde conduction over the accessory pathway, raising ventricular rate.[13] Rapid AV conduction can cause degeneration of atrial fibrillation or flutter into ventricular fibrillation and sudden death.[22]

Ventricular Arrhythmias. Calcium channel blockers are not effective in treating ventricular arrhythmias except when these arrhythmias occur in the context of coronary vasospasm with resultant myocardial ischemia. In this setting relief of ischemia through diminution of spasm may reduce the arrhythmia.

Hypertension

Available data suggest that nifedipine is effective in the therapy of chronic arterial hypertension. A regimen of 10 mg of nifedipine three or four times daily produces a mild to moderate decrease in arterial pressure.[1] Reflex-mediated increase in heart rate and plasma-renin activity seen with nifedipine are abolished by propranolol, which may also prolong nifedipine's antihypertensive action.[27] Nifedipine may be of particular value in patients with hypertension who also have angina or congestive heart failure. There is evidence to suggest that nifedipine 20 mg twice daily constitutes an effective antihypertensive regimen.[28] Widespread use of nifedipine in the treatment of hypertension awaits the development of a once-daily preparation.

The most obvious value of nifedipine therapy for hypertension has been seen in patients with hypertensive crisis. Sublingual administration of 10–20 mg results in an average decline in diastolic blood pressure of 20%. Nifedipine may be particularly

useful for treating hypertensive crisis when facilities for intensive hemodynamic monitoring are not available.[9]

Other uses of calcium channel-blocking agents

Calcium channel blockers are being investigated and used for many conditions, often involving excessive or abnormal vascular tone. Nifedipine has been tried, with limited success, in patients with primary pulmonary hypertension who generally do not respond well to any therapy. Verapamil is a useful supplement to beta blockers in treatment of hypertrophic cardiomyopathy, particularly in those patients who are not viewed as good surgical candidates. Nifedipine has been used as an afterload-reducing agent in treatment of congestive heart failure. It is probably most appropriate when ischemia, especially that secondary to vasospasm, contributes to failure. In chronic situations it has few advantages over more traditional vasodilators.

Calcium channel blockers have been studied as agents to limit myocardial damage during acute myocardial infarction and to decrease reinfarction rates. To date these investigations have not established any function for calcium channel blockers in these settings.

Calcium channel blockers are effective in treating Raynaud's phenomena. Nifedipine and diltiazem are both widely used for this purpose.

Nifedipine provides highly effective therapy for diffuse esophageal spasm and achalasia. It is also used for migraine headache prophylaxis, especially when agents such as propranolol and amitriptylene have proved ineffective. It is not helpful, however, in treatment of acute migraine episodes. Nifedipine has also been used in the setting of subarachnoid hemorrhage to prevent cerebral vasospasm.

Conclusions

Calcium channel blockers have a major part in the treatment of ischemic heart disease and supraventricular arrhythmias. They will soon be approved for the treatment of hypertension. Because these drugs are widely used and have distinct individual properties, the physician must be familiar with each of them in order to optimize therapy. ◉

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